

2. (Thrice Amended) A method for treatment or prophylaxis of toxin-induced peripheral neuropathy, comprising systemically administering to the patient an amount of a *hedgehog* polypeptide modified with one or more lipophilic moieties effective to treat or prophylactically treat toxin-induced peripheral neuropathy, wherein the *hedgehog* polypeptide comprises an amino acid sequence that a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and b) is identical to SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 14, or SEQ ID No: 15, or an N-terminal fragment thereof of at least 50 contiguous amino acid residues, and wherein said lipophilic modification comprises addition of one or more lipophilic moieties to the N-terminal amino acid residue.

6. (Thrice Amended) A method for the treatment or prophylaxis of virally induced peripheral neuropathy comprising systemically administering to a patient in need thereof an effective amount of a *hedgehog* polypeptide modified with one or more lipophilic moieties sufficient to treat or prophylactically treat virally induced peripheral neuropathy, wherein the *hedgehog* polypeptide comprises an amino acid sequence that a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and b) is identical to SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 14, or SEQ ID No: 15, or an N-terminal fragment thereof of at least 50 contiguous amino acid residues, and wherein said lipophilic modification comprises addition of one or more lipophilic moieties to the N-terminal amino acid residue.

10. (Thrice Amended) The method of claim 2 or 6, wherein the *hedgehog* amino acid sequence is encodable by a nucleic acid which hybridizes under stringent conditions, including a wash step of 0.2X SSC at 65 °C, to at least one of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6.

11. (Thrice Amended) The method of claim 10, wherein the *hedgehog* amino acid sequence is a vertebrate *hedgehog* polypeptide.

13. (Thrice Amended) The method of claim 10, wherein the polypeptide includes at least a 50 amino acid extracellular portion of a vertebrate *hedgehog* polypeptide selected from at least one of SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 14, or SEQ ID No: 15.

14. **(Thrice Amended)** The method of claim 10, wherein the polypeptide includes at least a 150 amino acid extracellular portion of a vertebrate *hedgehog* polypeptide selected from at least one of SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 14, or SEQ ID No: 15.
15. **(Thrice Amended)** The method of claim 10, wherein the polypeptide includes at least an extracellular portion of a vertebrate *hedgehog* polypeptide corresponding to residues 24-194 of SEQ ID No:15.
19. **(Amended)** The method of claim 10, wherein the polypeptide is modified with one or more fatty acid moieties.
20. **(Reiterated)** The method of claim 19, wherein each fatty acid moiety is independently selected from myristoyl, palmitoyl, stearoyl, or arachidoyl.
21. **(Amended)** The method of claim 10, wherein the polypeptide is modified with one or more aromatic hydrocarbons.
22. **(Reiterated)** The method of claim 21, wherein each aromatic hydrocarbon is independently selected from benzene, perylene, phenanthrene, anthracene, naphthalene, pyrene, chrysene, or naphthacene.
23. **(Amended)** The method of claim 10, wherein the polypeptide is modified one or more times with a C7 - C30 alkyl or cycloalkyl.
30. **(Amended)** The method of claims 2 or 6, wherein the *hedgehog* agonist mimics *hedgehog* signal transduction by altering the localization, protein-protein binding and/or enzymatic activity of an intracellular protein involved in *hedgehog* signaling.
31. **(Amended)** The method of claims 2 or 6, wherein the *hedgehog* agonist alters the level of expression of a *hedgehog* protein, a *patched* protein or a protein involved in *hedgehog* signal transduction.

41. (Amended) The method of claims 2 or 6, wherein the patient is being treated prophylactically.
46. (Amended) The method of claim 2, wherein the toxin-induced neuropathy is due to contact with a chemotherapeutic agent.
51. (Thrice Amended) The method of claim 10, wherein the polypeptide is a fusion protein.
55. (Twice Amended) The method of claim 10, wherein the N-terminal fragments have a molecular weight of about 19 kD.

The amended claims are re-stated below to reflect changes with respect to the last filing.

2. (Thrice Amended) A method for treatment or prophylaxis of toxin-induced peripheral neuropathy, comprising systemically administering to the patient an amount of a *hedgehog* polypeptide modified with ~~two~~ one or more lipophilic moieties effective to treat or prophylactically treat toxin-induced peripheral neuropathy, wherein the hedgehog polypeptide comprises an amino acid sequence that a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and b) is ~~at least 80%~~ identical to ~~at least one of~~ SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 14, or SEQ ID No: 15, or an N-terminal fragment thereof of at least 50 contiguous amino acid residues, and wherein said lipophilic modification comprises addition of ~~two~~ one or more lipophilic moieties to ~~an~~ the N-terminal amino acid residue.
6. (Thrice Amended) A method for the treatment or prophylaxis of virally induced peripheral neuropathy comprising systemically administering to a patient in need thereof an effective amount of a *hedgehog* polypeptide modified with ~~two~~ one or more lipophilic moieties sufficient to treat or prophylactically treat virally induced peripheral neuropathy, wherein the hedgehog polypeptide comprises an amino acid sequence that a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and b) is ~~at least 80%~~ identical to ~~at least one of~~ SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 14, or SEQ ID No: 15, or an N-

terminal fragment thereof of at least 50 contiguous amino acid residues, and wherein said lipophilic modification comprises addition of ~~two~~ one or more lipophilic moieties to ~~an~~ the N-terminal amino acid residue.

10. **(Thrice Amended)** The method of claim 2 or 6 9, wherein the *hedgehog* amino acid sequence is encodable by a nucleic acid which hybridizes under stringent conditions, including a wash step of 0.2X SSC at 65 °C, to at least one of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6.

11. **(Thrice Amended)** The method of claim 10 9, wherein the *hedgehog* amino acid sequence is a vertebrate *hedgehog* polypeptide.

13. **(Thrice Amended)** The method of claim 10 9, wherein the polypeptide includes at least a 50 amino acid extracellular portion of a vertebrate *hedgehog* polypeptide selected from at least one of SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 14, or SEQ ID No: 15.

14. **(Thrice Amended)** The method of claim 10 9, wherein the polypeptide includes at least a 150 amino acid extracellular portion of a vertebrate *hedgehog* polypeptide selected from at least one of SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 14, or SEQ ID No: 15.

15. **(Thrice Amended)** The method of claim 10 9, wherein the polypeptide includes at least an extracellular portion of a vertebrate *hedgehog* polypeptide corresponding to residues 24-194 of SEQ ID No:15.

19. **(Amended)** The method of claim 10 46, wherein the polypeptide is modified with one or more fatty acid moieties.

21. **(Amended)** The method of claim 10 46, wherein the polypeptide is modified with one or more aromatic hydrocarbons.

23. **(Amended)** The method of claim 10 46, wherein the polypeptide is modified one or more times with a C7 - C30 alkyl or cycloalkyl.

30. (Amended) The method of ~~any of~~ claims 2 or 6 ~~1-6~~, wherein the *hedgehog* agonist mimics *hedgehog* signal transduction by altering the localization, protein-protein binding and/or enzymatic activity of an intracellular protein involved in *hedgehog* signaling.

31. (Amended) The method of ~~any of~~ claims 2 or 6 ~~1-6~~, wherein the *hedgehog* agonist alters the level of expression of a *hedgehog* protein, a *patched* protein or a protein involved in *hedgehog* signal transduction.

41. (Amended) The method of ~~any of~~ claims 2 or 6 ~~4-6~~, wherein the patient is being treated prophylactically.

46. (Amended) The method of claim 2 44, wherein the toxin-induced neuropathy is due to contact with a ~~toxic~~ chemotherapeutic agent.

51. (Thrice Amended) The method of claim 10 9, wherein the polypeptide is a fusion protein.

55. (Twice Amended) The method of claim 10 9, wherein the N-terminal fragments have a molecular weight of about 19 kD.

REMARKS

Claims 1-73 are the pending claims in the present application. Applicants will cancel non-elected claims upon indication of allowable subject matter. Please cancel, without prejudice, claims 1, 3, 4, 5, 9, 17, 18, 44, 45, 47, 48, 50, 52, 53, and 59-73. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1-4. Applicants note with appreciation that the request for a Continued Prosecution Application is acceptable, and that the amendments put forth in Paper 28 have been entered in full.